

Diabetic Nephropathy

By

Fatma El-Husseiny Moustafa

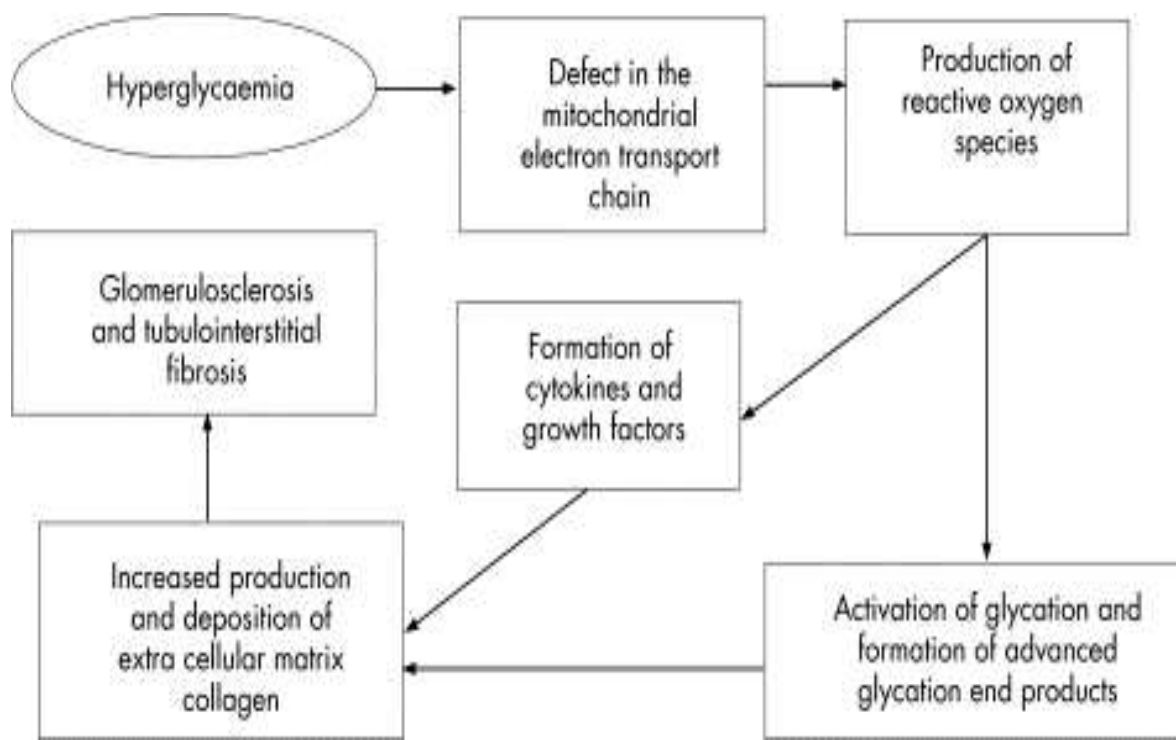
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- Approximately a third of patients with type 1 insulin-dependent diabetes mellitus (IDDM) and type 2 non-insulin-dependent diabetes mellitus (NIDDM) develop diabetic nephropathy.

Pathogenesis of Diabetic glomerulopathy

- The pathologic hallmark of diabetic nephropathy is diabetic glomerulosclerosis
- Diabetic glomerulopathy seems a consequence of persistently high concentration of glucose in the blood, which stimulates increased production and decreased degradation of mesangial matrix and glomerular basement membrane components,
- that results in progressive increase in extracellular matrix in the glomerular mesangium and glomerular basement membranes with subsequent thickening of basement membrane and accentuation of mesangial matrix.



	DM Type I	DM Type II
Nephropathy	10 to 15 years after the onset	after 5 to 10 years
Retinopathy	all or at least 80% of patients	50-60% of patients
Hypertension	20-40%	50%

Indications of Kidney Biopsy in Diabetic Patients with Renal Disease

- Nephrotic syndrome appearing less than 10yrs of DM diagnosis (type I)
- Absence of retinopathy or neuropathy (type I)
- Atypical clinical renal features - sudden onset of NS, hematuria, rapid onset of renal failure, unexplained renal failure.
- Serologic & Systemic evidence of infection, autoimmune disease or small vessel vasculitis

Biopsy is done to:

- To establish the diagnosis of diabetic nephropathy, correlate with clinical renal disease
- To detect existence of non-diabetic renal disease

Pathologic Classification of Diabetic Nephropathy

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Arthur H. Cohen[‡], H. Terence Cook[§], Cinthia B. Drachenberg^{||},
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Published online before print
February 18, 2010, doi:
10.1681/ASN.2010010010

JASN April 1, 2010 vol. 21 no. 4
455-464

Glomerular Classification of DN

Tervaert TWC et al, J Am Soc Nephrol 2010

Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes, Mild basement membrane thickening and EM-proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV. GBM > 395nm in female and >430nm in male. individuals 9yrs of age or older
II	Mild mesangial expansion IIA	Biopsy does not meet criteria for class III or IV. <u>Mild mesangial expansion</u> in >25% of the observed mesangium.
	Severe mesangial expansion IIB	Biopsy does not meet criteria for class III or IV. <u>Severe mesangial expansion</u> in >25% of the observed mesangium.
III	Nodular sclerosis (Kimmelstiel-Wilson lesion)	At least one convincing Kimmelstiel-Wilson lesion. Biopsy does not meet criteria for class IV. Global glomerular sclerosis in <50% of glomeruli.
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli. Lesions from classes I through III

Diabetic Nephropathy

■ Glomerular

- Thickening of glomerular basement membrane (GBM)
- Mesangial expansion
- Nodular glomerulosclerosis (Kimmelstiel-Wilson lesions)
- Global glomerular sclerosis

■ Tubulo- interstitial

- Thickening of tubular basement membrane (TBM)

■ Vascular

- Hyalinization of afferent & efferent arterioles

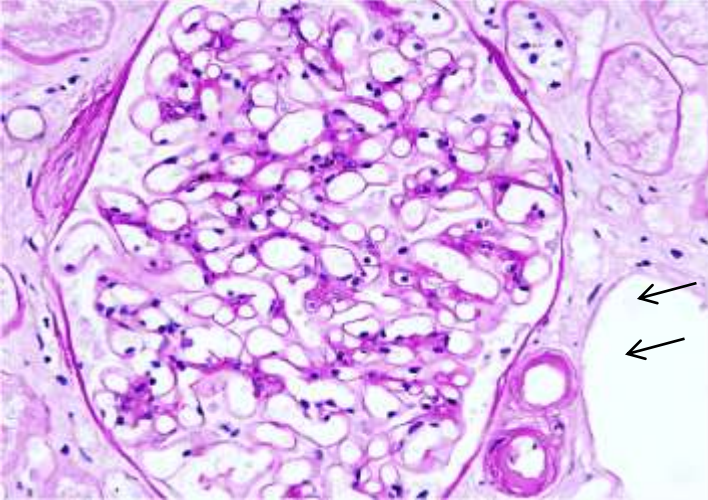
Biopsy prerequisites for proper classification

- Biopsies should contain at least 10 glomeruli excluding incomplete glomeruli along the biopsy edge.
- Immunofluorescence requires the use of antibodies against IgA, IgG, IgM, C3, C1q, Albumin, kappa and lambda light chains to rule out other renal diseases.
- Electron microscopy (EM) must be performed especially in class I

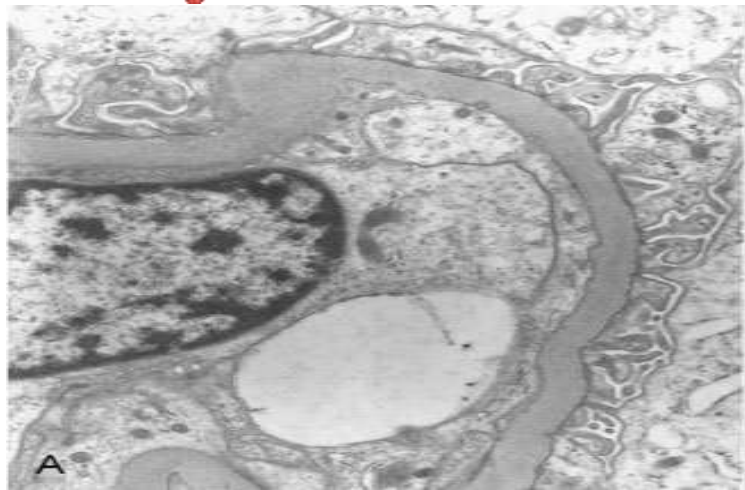
Class I

Glomerular Basement Membrane Thickening

- Biopsy shows **no** or **only mild basement membrane thickening** , nonspecific changes by light microscopy
- **Changes do not meet the criteria of classes II through IV**
 - Absence of mesangial expansion,
 - nodular KW lesions and
 - glomerulosclerosis
- **GBM**, measured with EM is, on average
 - Thicker than 430 nm in males
 - Thicker than 395 nm in females

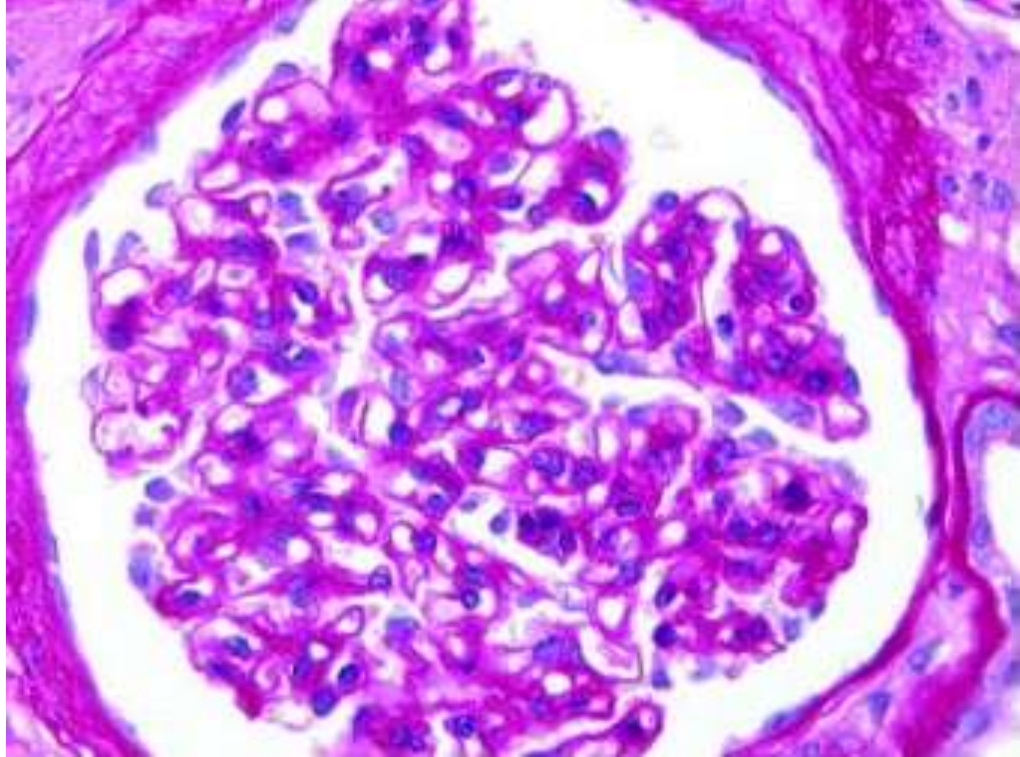


Class I
GBM Thickening
Absence of mesangial expansion,
Kimmelsteil-Wilson lesions, or global
glomerulosclerosis



No mesangial matrix expansion or BM
 thickening by L/M
 Note arteriolar intimal hyalinization

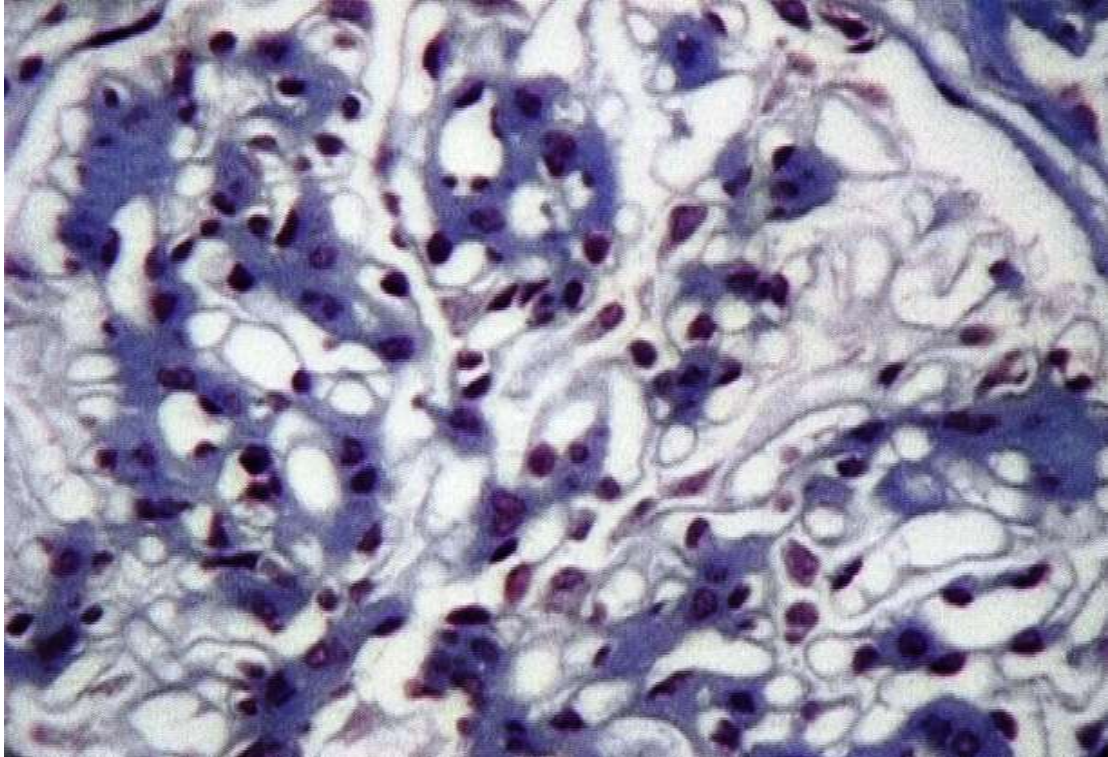
**Class I Mid
Thickening of
basement
membranes**



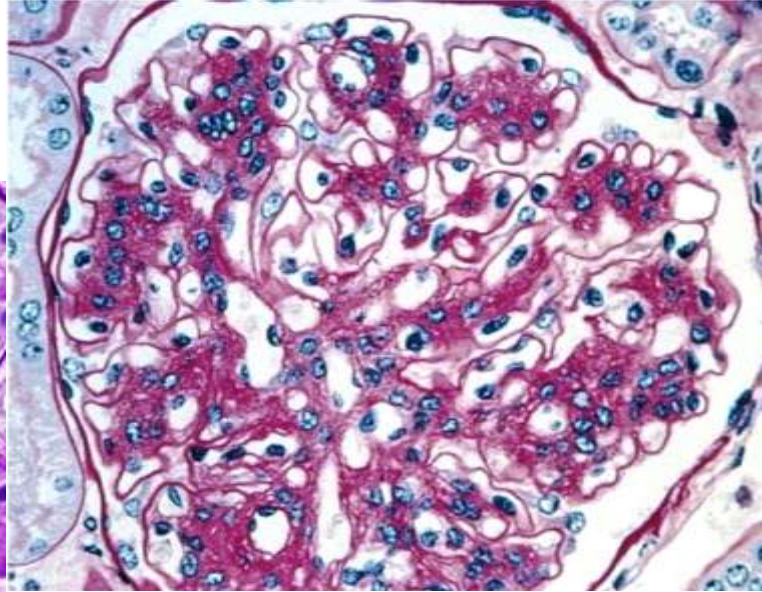
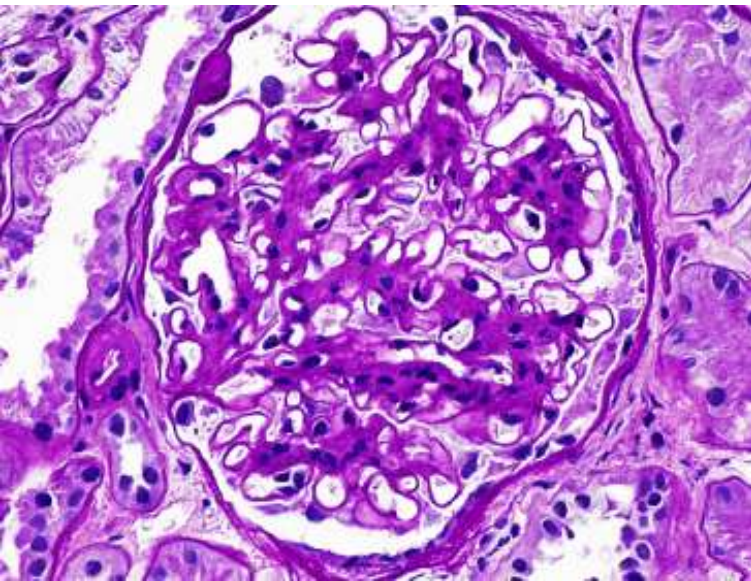
Class II

- **Mesangial expansion** – increase in extracellular material in the mesangium such that the width of the interspace *exceeds two mesangial cell nuclei* in at least two glomerular lobules
 - II a – **Mild** – expanded mesangial area \leq mean area of a capillary lumen
 - II b – **Severe** - expanded mesangial area $>$ mean area of a capillary lumen
- Biopsy not meeting the criteria for class III or IV i.e. No nodular or global sclerosis.

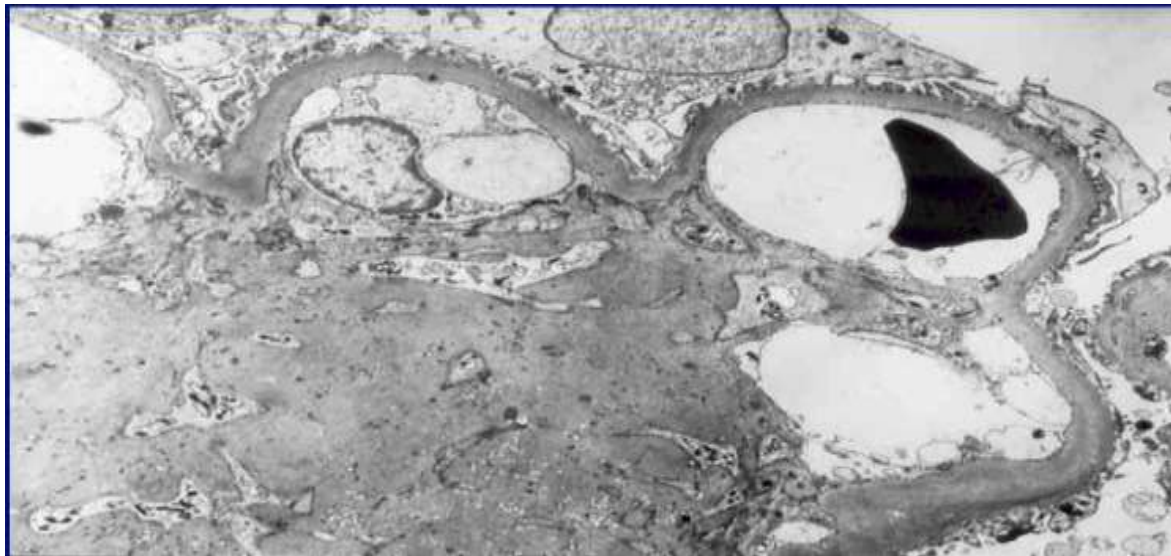
Class IIA



Class IIb



Expanded mesangial matrix



Class III

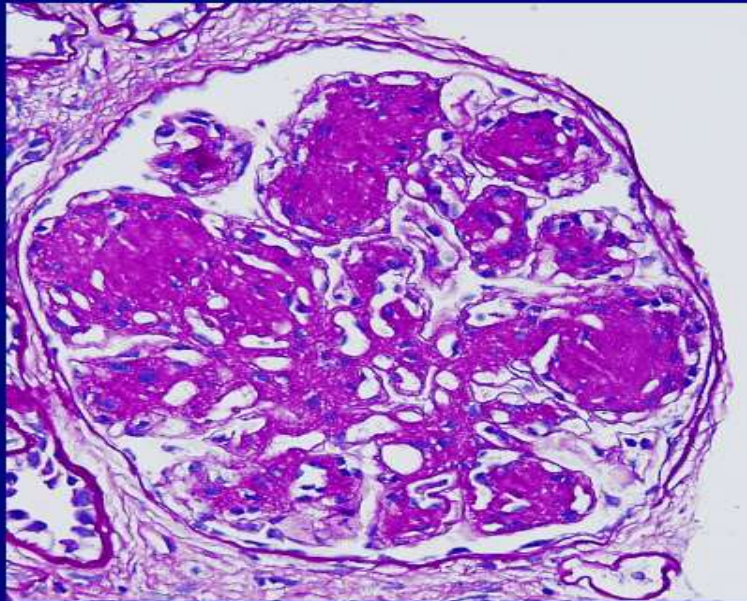
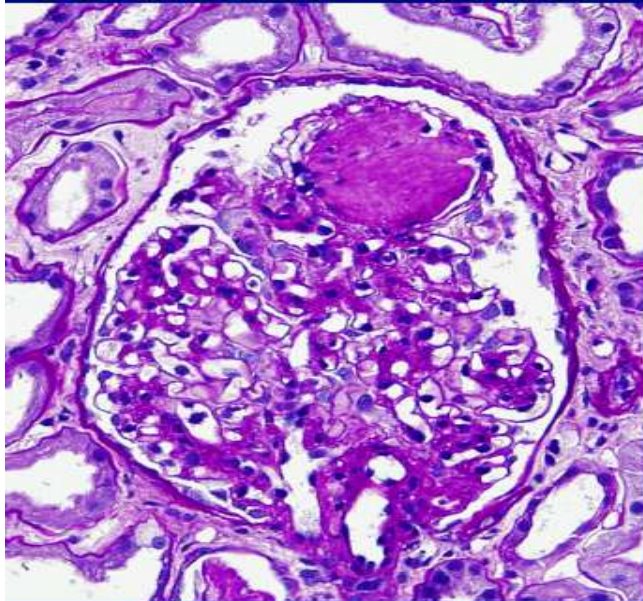
■ Nodular Sclerosis – Kimmelstiel-Wilson lesions.

- At **least one** convincing Kimmelstiel-Wilson lesion is found
- The biopsy specimen **does not have** more than 50% global glomerulosclerosis (Class III)

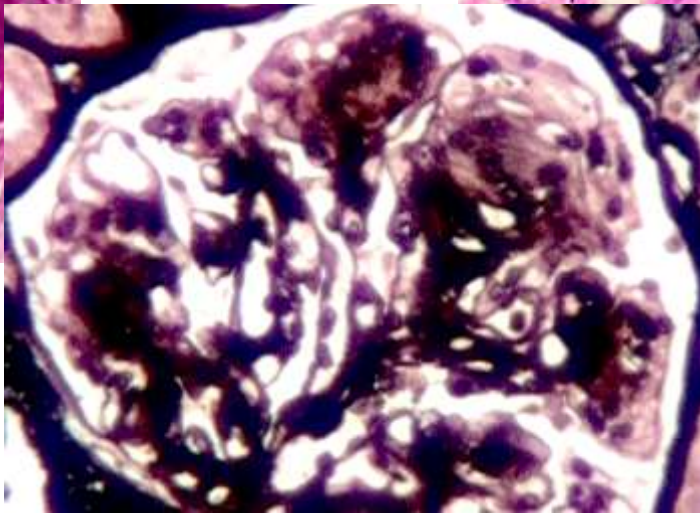
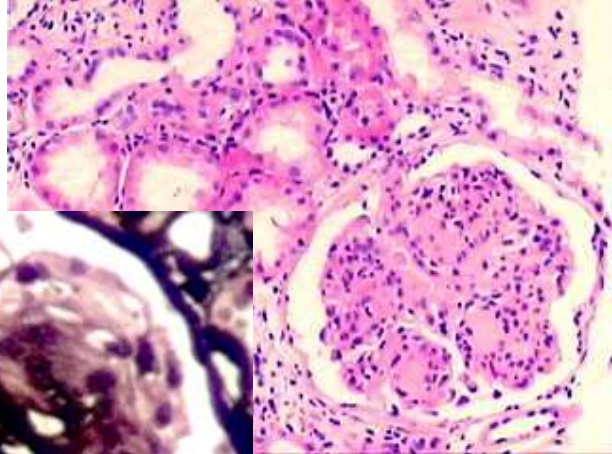
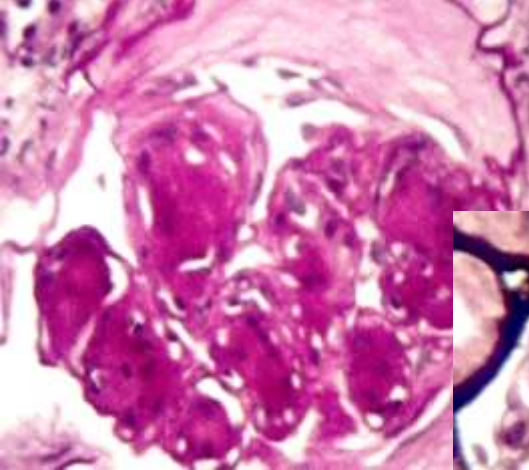
Kimmelstiel-Wilson Nodule

- The nodules begin in the heart of the mesangial region of a segment. As the nodule increases there may be increased numbers of mesangial cells, especially at its leading edges . The nodules often are focal and segmental, although occasional specimens have rather diffuse global nodularity.
- The nodules have the same tinctorial properties as normal mesangial matrix and thus are PAS and silver positive . The matrix at the center of the nodules may be homogeneous or laminated
- K–W nodules may have a corona of capillary aneurysms that are formed as a result of mesangiolysis, which disrupts the attachment points of the GBM to the mesangium.

Kimball-Wilson lesion – focal, lobular, round to oval mesangial lesions with acellular, hyaline/matrix core, rounded peripherally arranged crescent-shaped mesangial nuclei



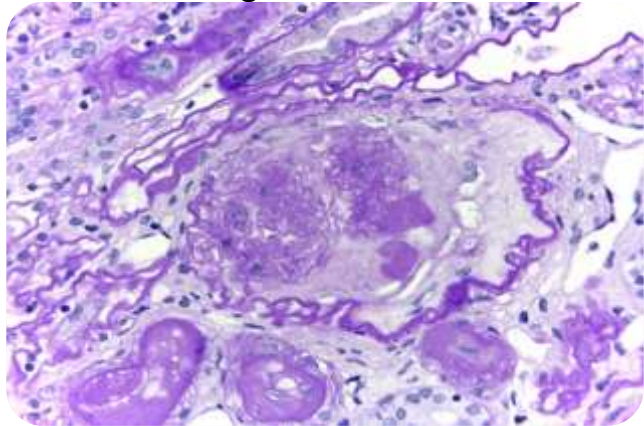
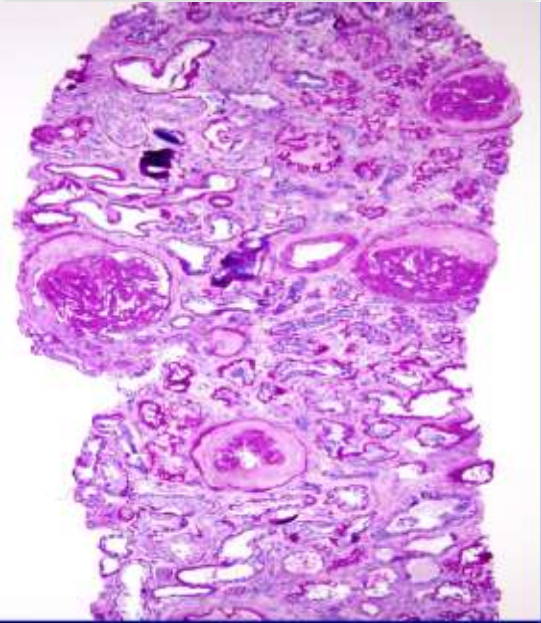
Class III



Class IV

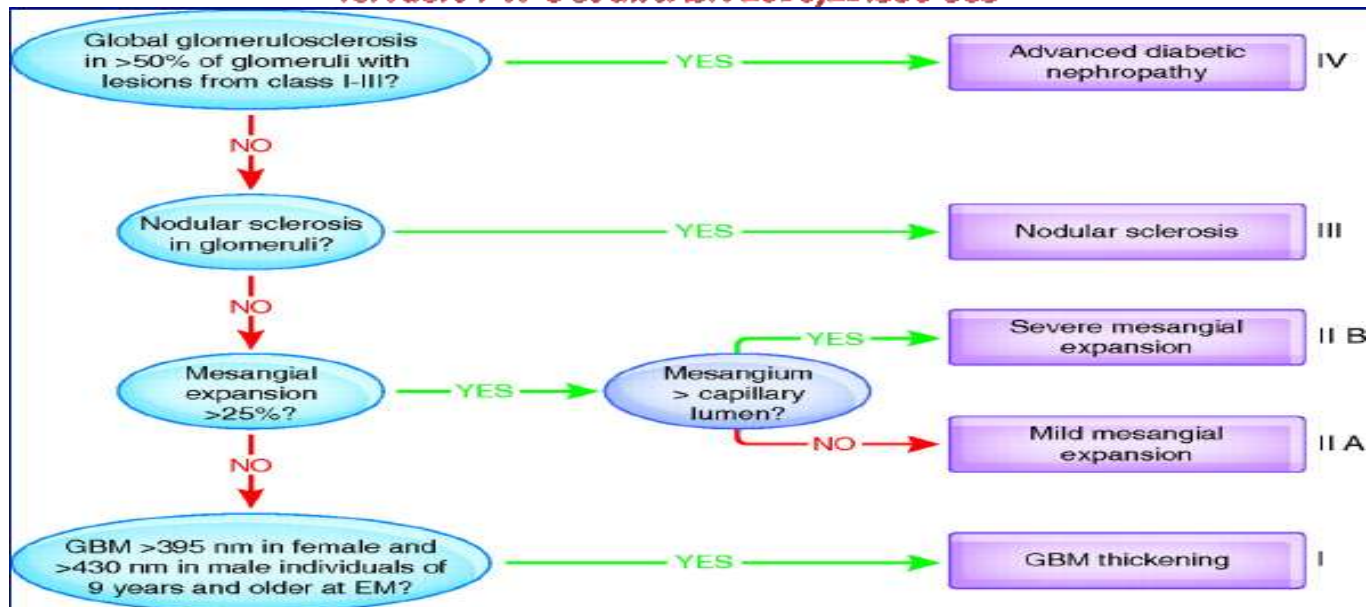
Advanced Diabetic Glomerulosclerosis

- **Advanced DN**
- **More than 50%** global glomerulosclerosis
- There is clinical or pathological evidence that the sclerosis is attributable to DN
- Glomerulosclerosis without evidence for DN will not be assigned this class.



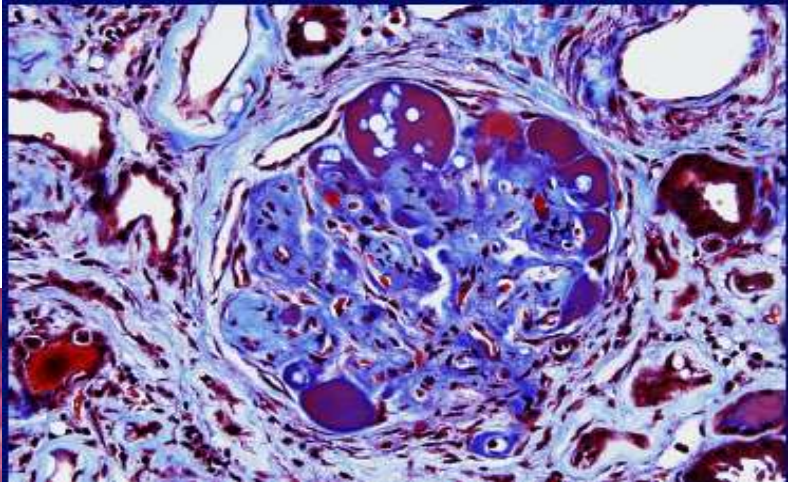
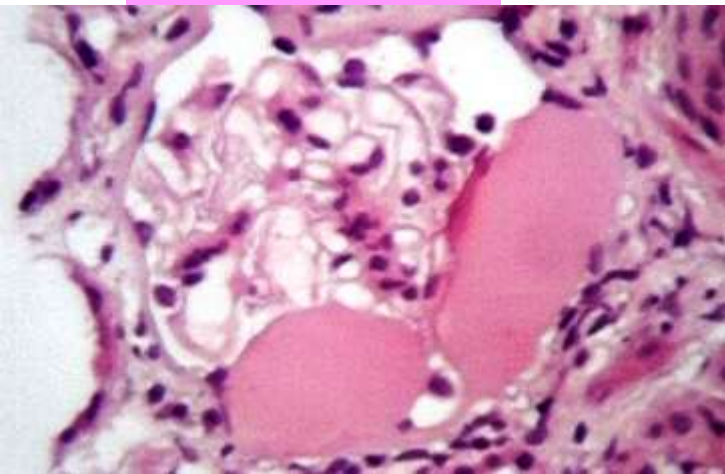
Flow chart for classifying DN.

Tervaert T W C et al. JASN 2010;21:556-563

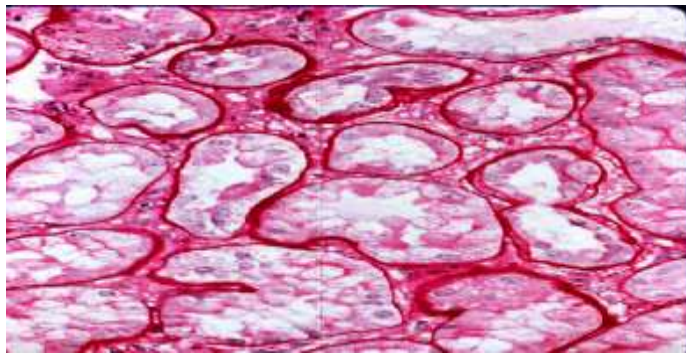


Hyaline lesions of diabetic nephropathy

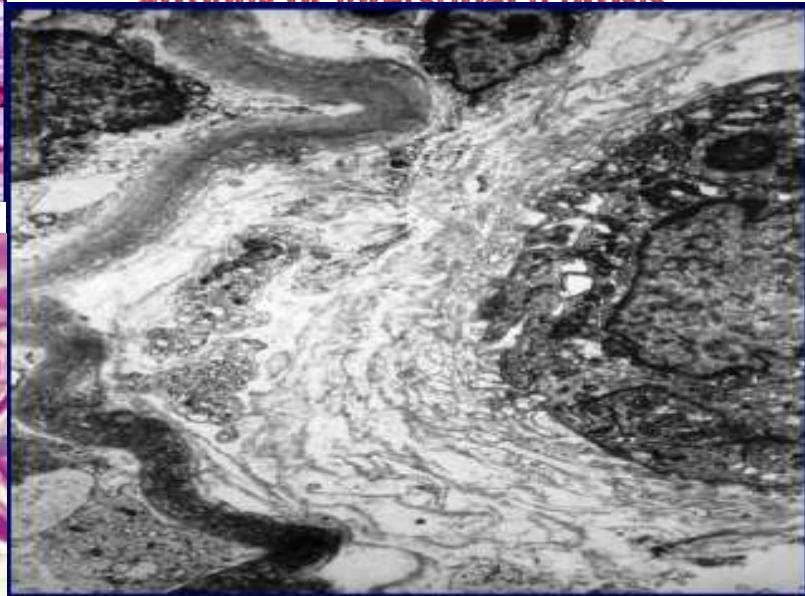
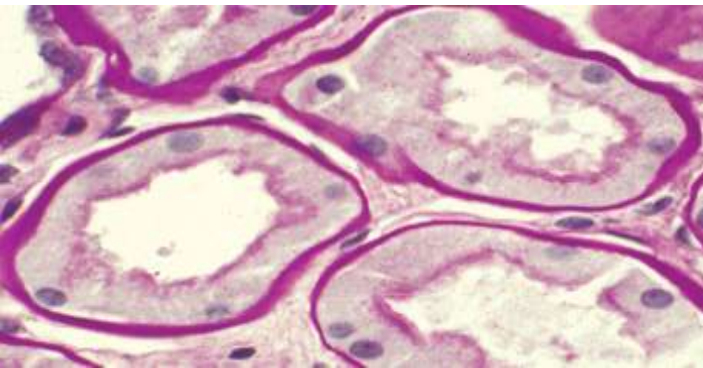
Capsular drop



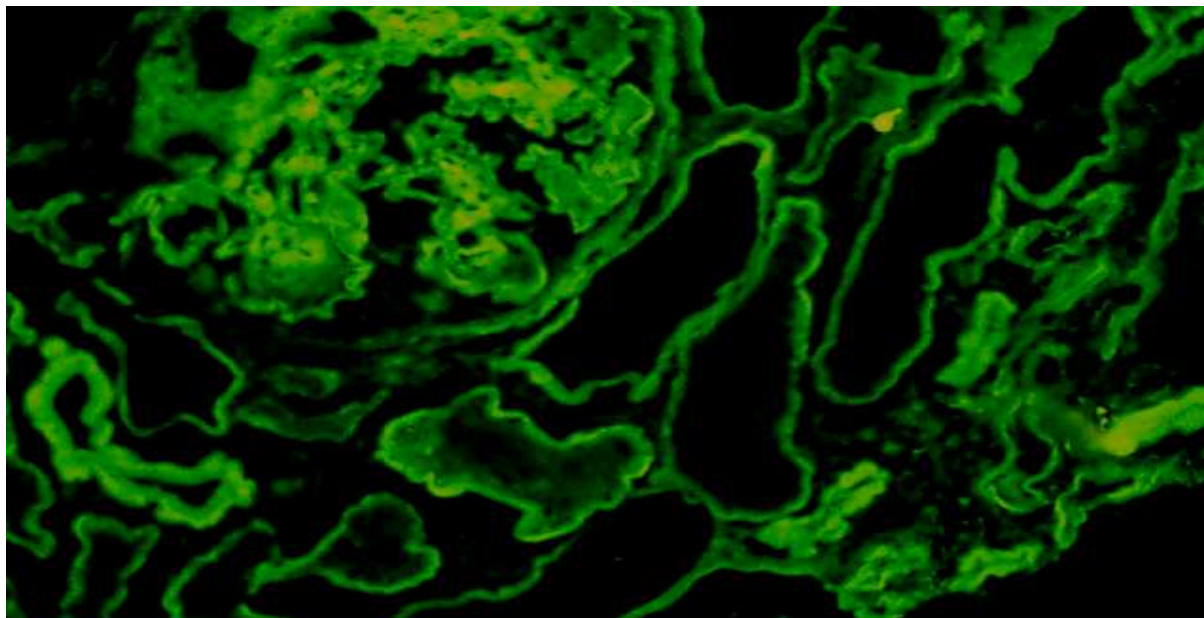
Hyaline cap



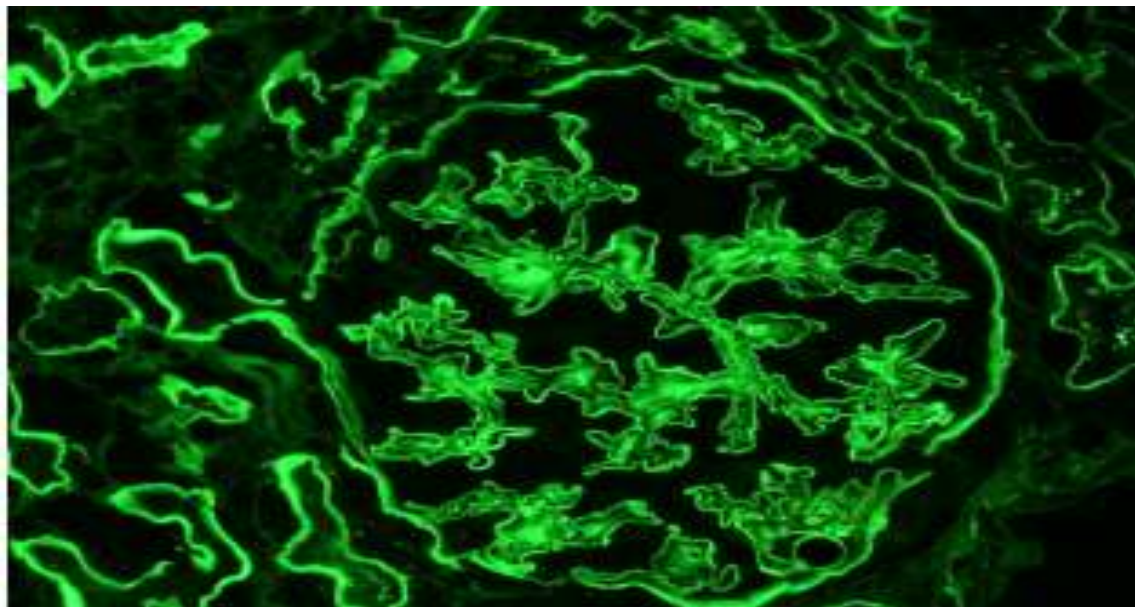
**Thickened tubular basement
membrane even
though there is no tubular
atrophy or interstitial fibrosis**



Immunofluorescence microscopy linear positive for IgG



Linear labeling of GBM with FITC conjugated anti-albumin antibody



Pathologic differential diagnosis

Pathologic differential diagnosis

- Class I:

1. Minimal change disease
2. Membranous nephropathy



- Class II: Other causes of mesangial thickening (Fibrillary GN)

- Class III:

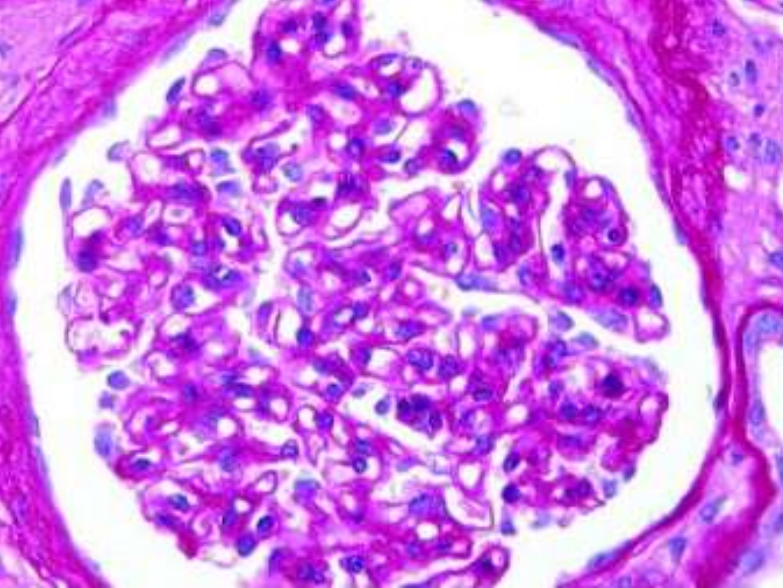
1. Membranoproliferative pattern of GN
2. Amyloidosis
3. Light chain nephropathy

- Class IV:

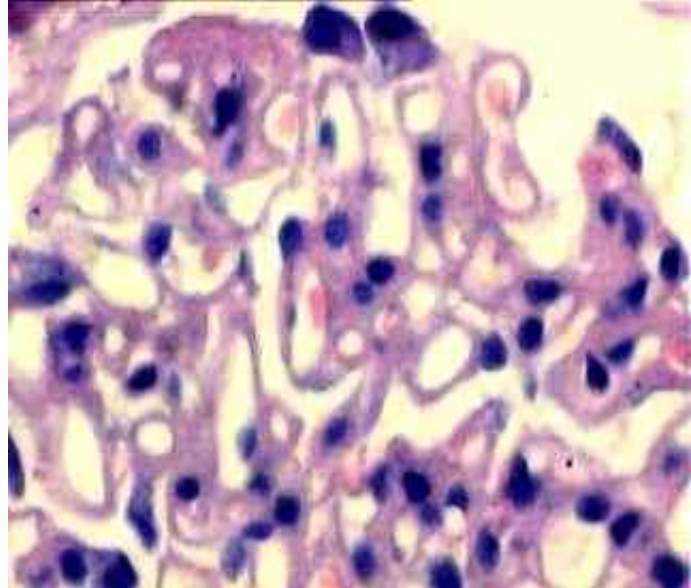
1. Hypertensive renal disease
2. Advanced non diabetic renal disease

1- Minimal change disease

	Diabetic nephropathy Class I	Minimal change disease
effacement of foot processes	\pm	+
immunofluorescence	Linear GBM and TBM with albumin and IgG	-ve

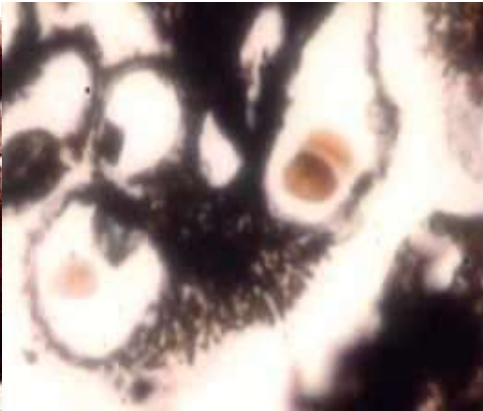
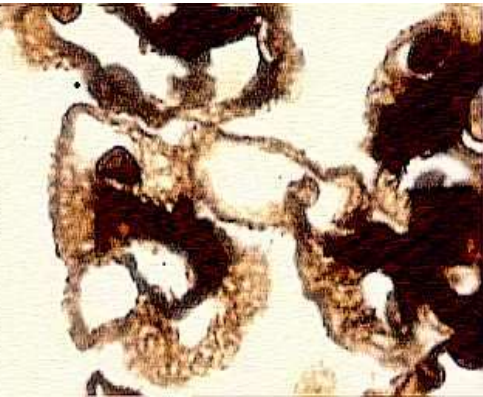
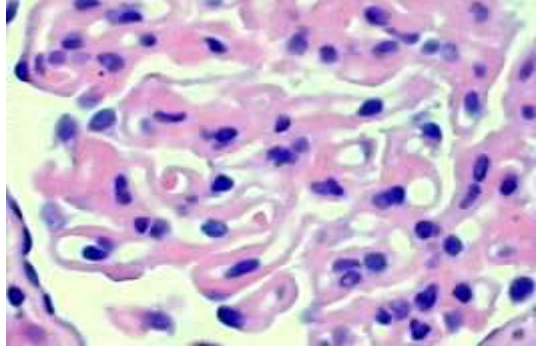
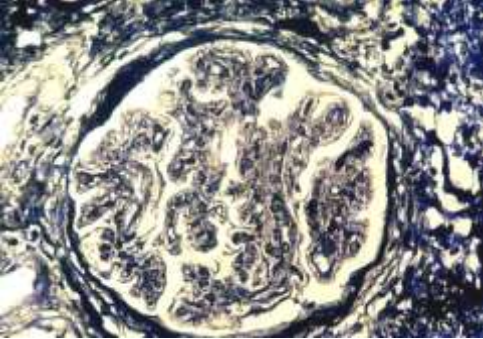


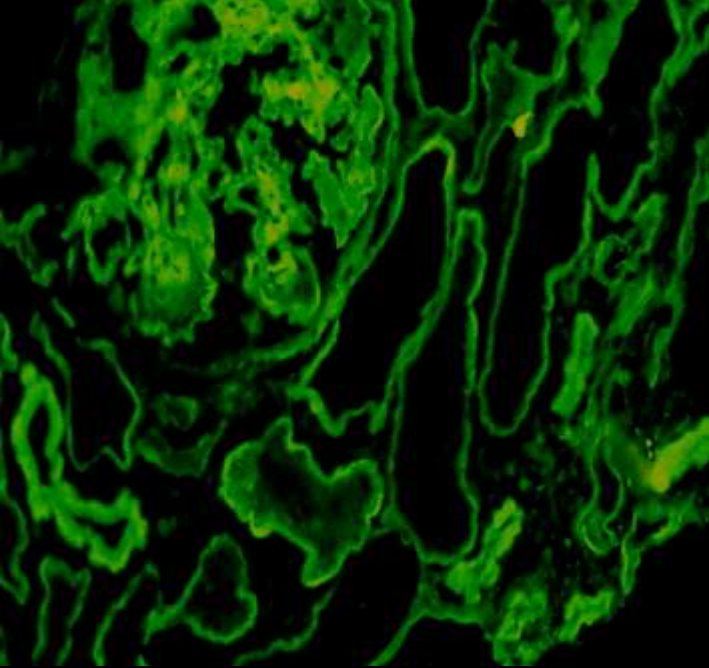
Diabetic nephropathy Class I



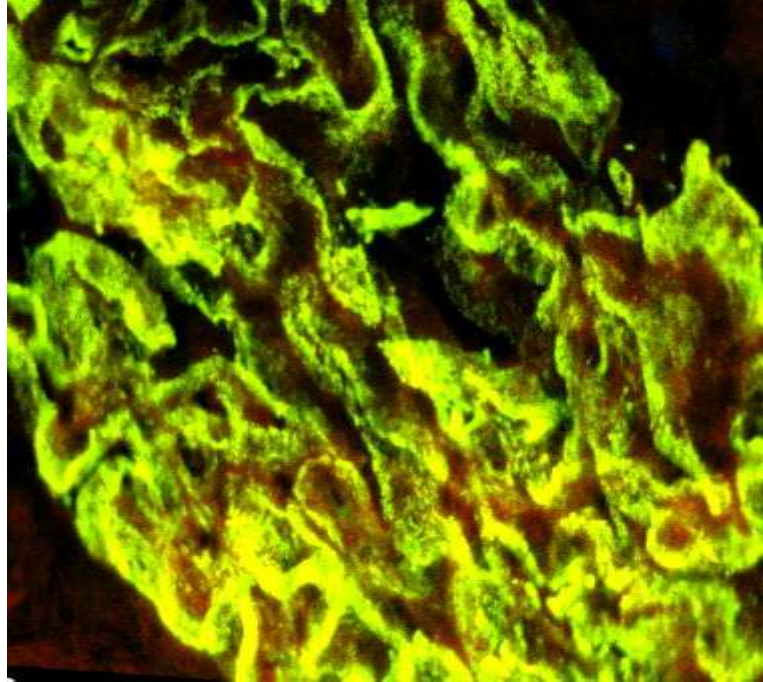
Membranous nephropathy

Membranous nephropathy



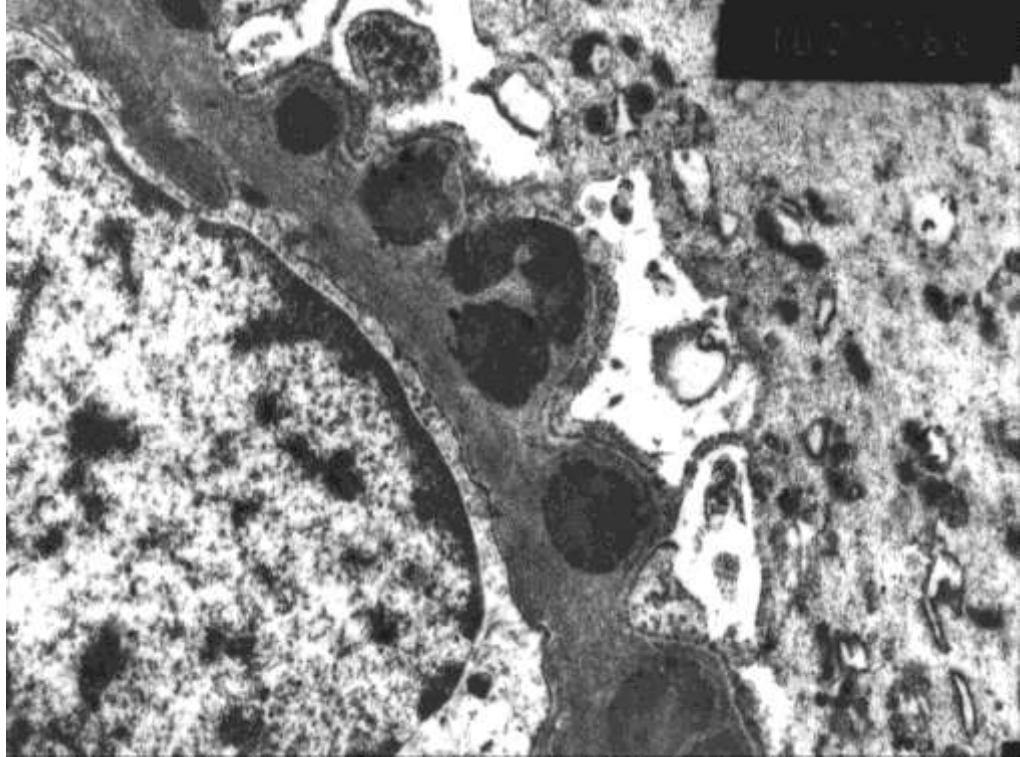


Diabetic linear GBM & TBM pattern for IgG.



Membranous nephropathy Finely granular IgG deposits

**Membranous
nephropathy
electron dense
deposits**



2- Membranous nephropathy

	Diabetic nephropathy	Membranous nephropathy
Spikes & vacuolisation seen by Silver stain	–	+
IF IgG & Albumin	linear GBM & TBM pattern for both albumin & IgG.	typical granular deposits of IgG exclusively in glomeruli, along the capillary walls -ve albumin deposits
Electron dense deposits	–	+ subepithelial deposits

Pathologic differential diagnosis

- Class I:
 1. Minimal change disease
 2. Membranous nephropathy
- Class II: Other causes of mesangial thickening (Fibrillary GN) ←
- Class III:
 1. Membranoproliferative pattern of GN
 2. Amyloidosis
 3. Light chain nephropathy
- Class IV:
 1. Hypertensive renal disease
 2. Advanced non diabetic renal disease

FIBRILLARY GLOMERULOPATHIES

Congo red

+

-

AMYLOID

NON - AMYLOID

Immunofluorescence

+

-

Immunoglobulin
Derived

Non-immunoglobulin
Derived

Diabetes Mellitus

Cryo-
globulinemia

Monoclonal
Gammopathy

Systemic Lupus
Erythematosus

Immunotactoid
Glomerulopathy

CLL
Mixed Essential
Multiple Myeloma

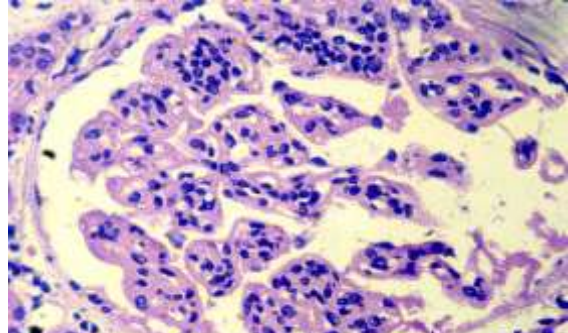
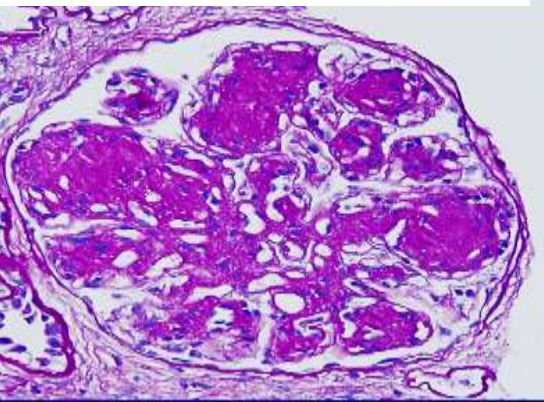
"Benign"
CLL
LCDD
Multiple Myeloma

Pathologic differential diagnosis

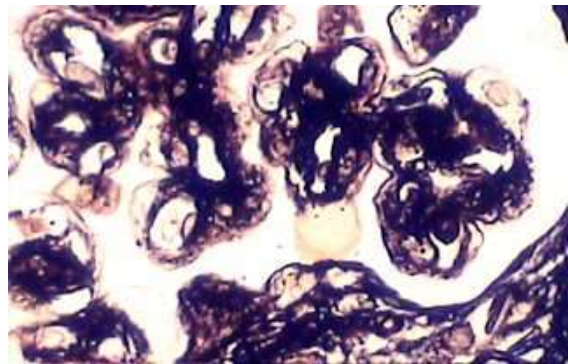
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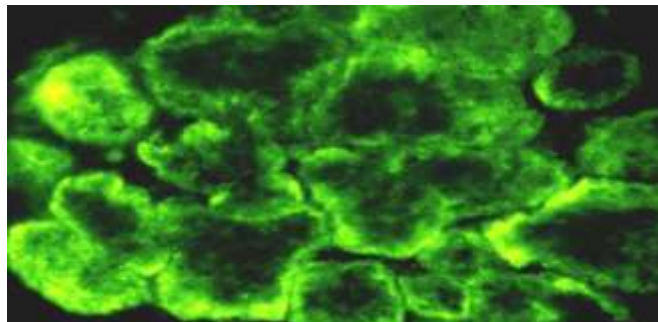
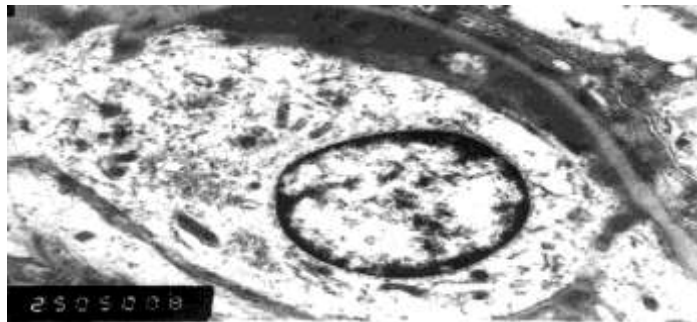
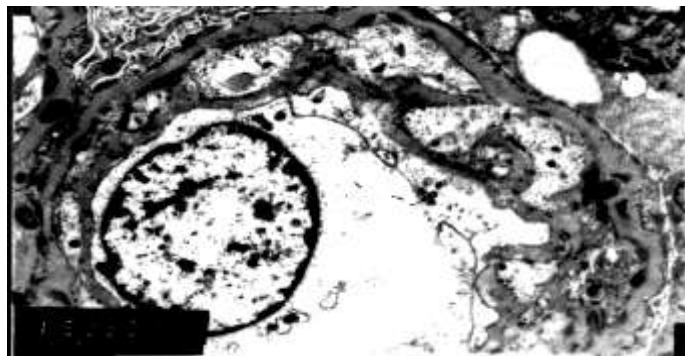


Diabetic nephropathy Class III



Membranoproliferative GN





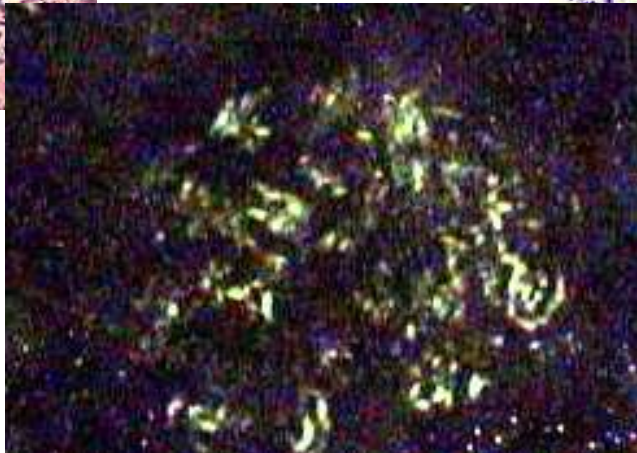
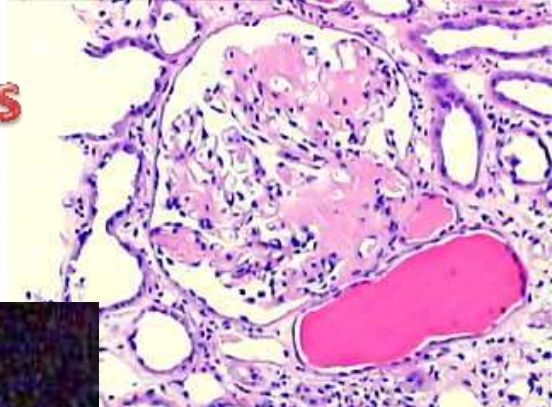
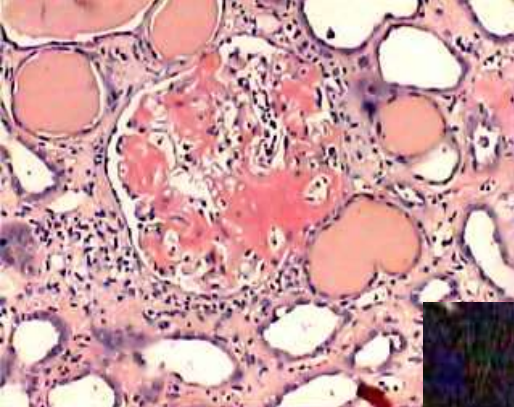
Membranoproliferative glomerulonephritis type I

	Diabetic Nephropathy	MPGN
hypercellularity	±	+
circumferential mesangial cell interposition	-	+
Double contoured appearance by silver stain	-	+
Subendothelial & mesangial deposits	+	-
linear GBM & TBM pattern for both albumin & IgG	+	-

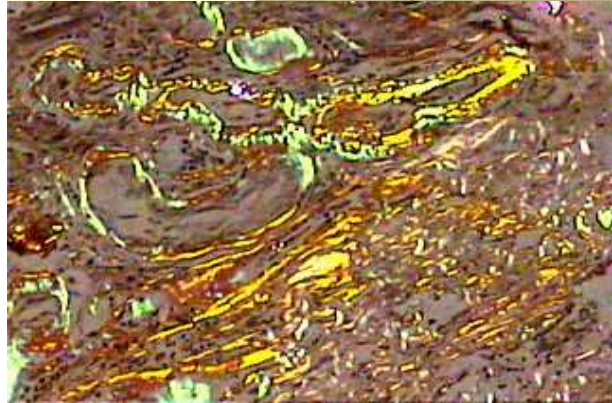
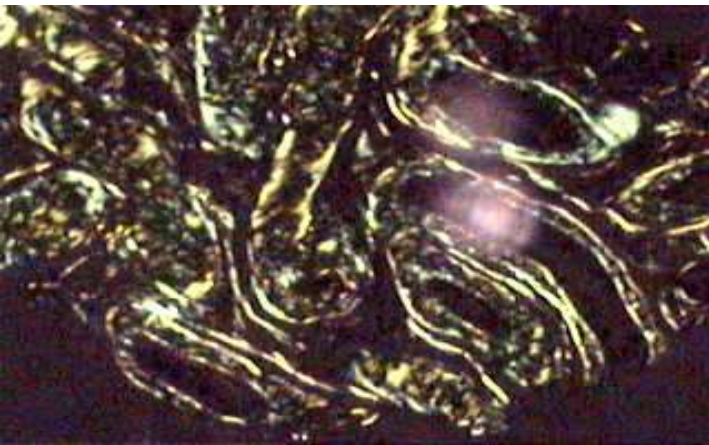
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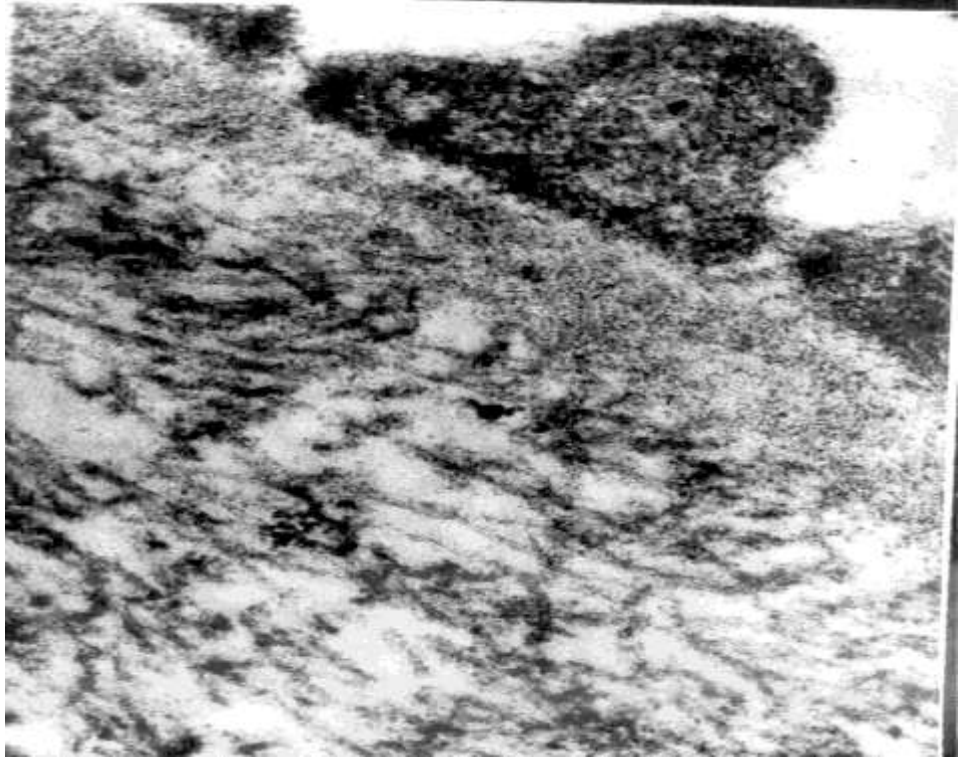
Amyloidosis



Amyloidosis



Amyloid fibrils



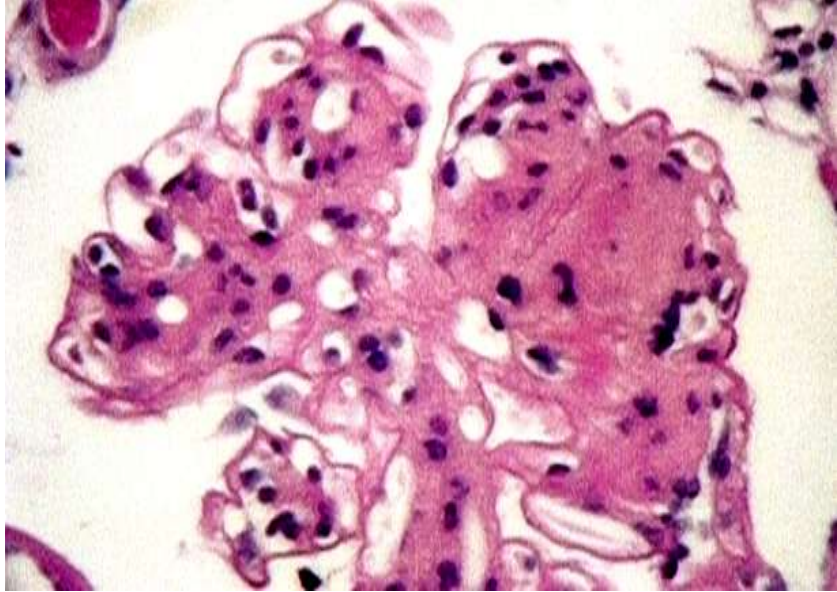
Amyloidosis

	Diabetic Nephropathy Class III	Amyloidosis
silver staining	+	-
Congo red	-	+
Electron microscopy	Increased mesangial matrix	long, unbranching filaments

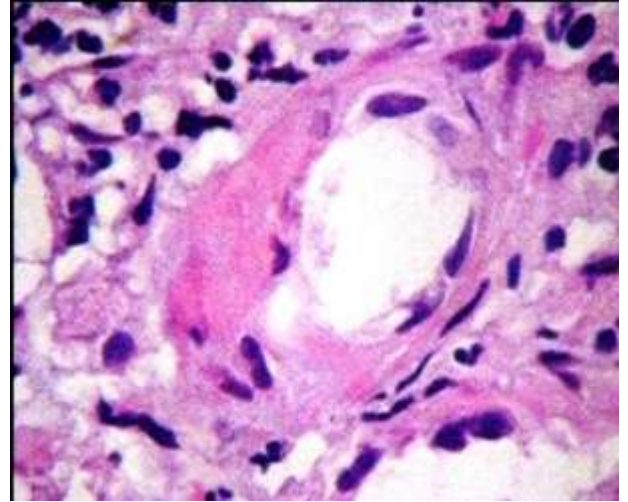
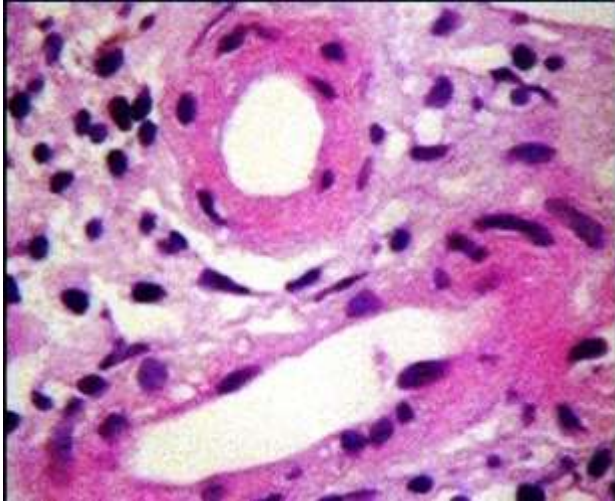
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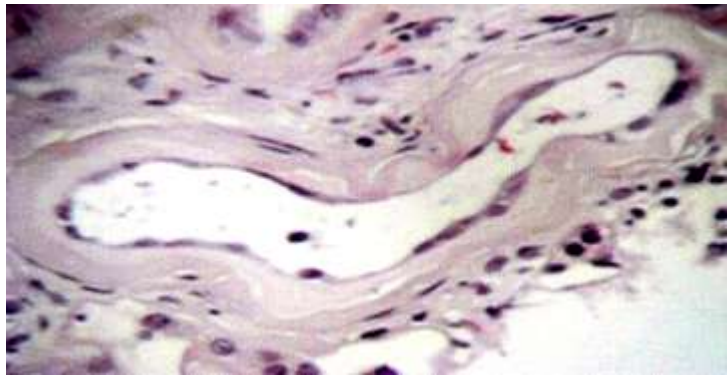
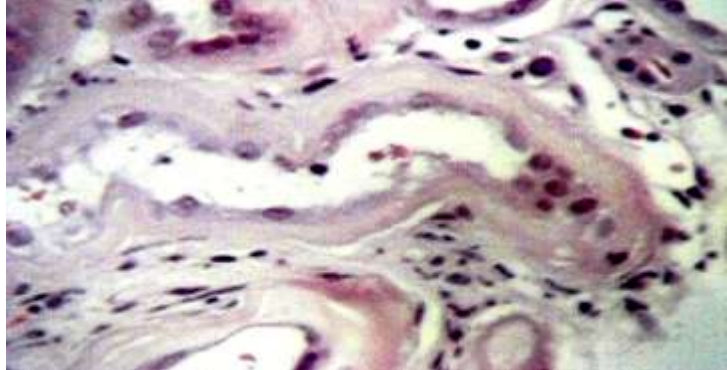
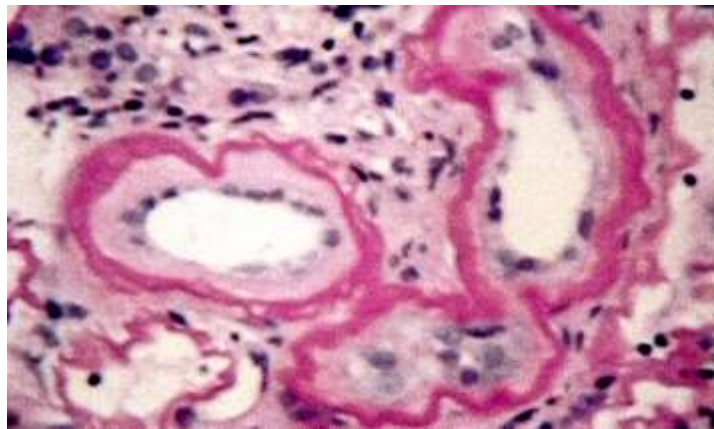
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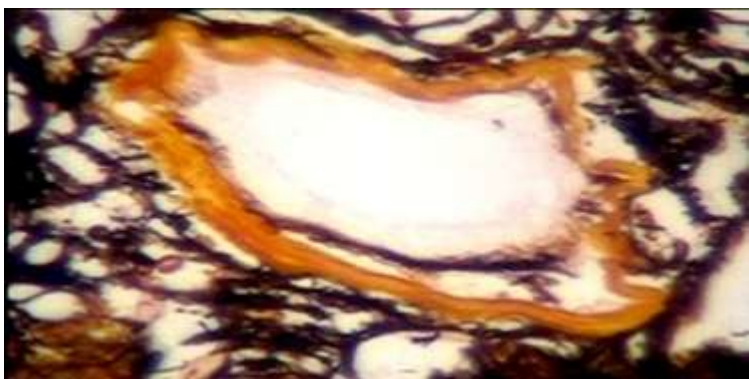
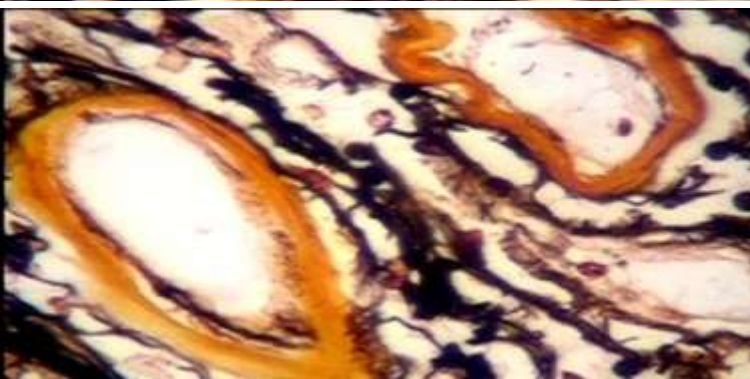
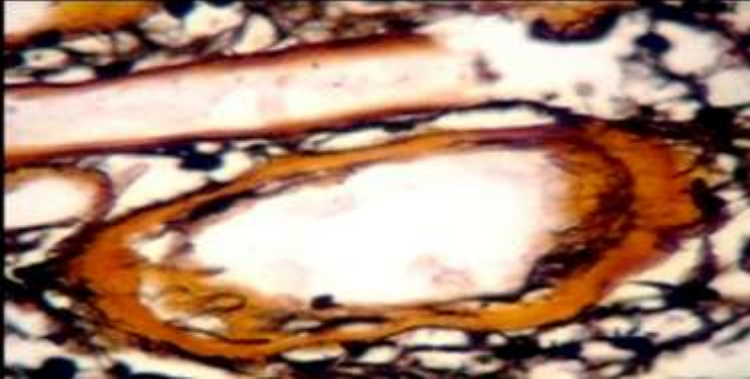
**Nodular glomerular lesion
in light chain
nephropathy**

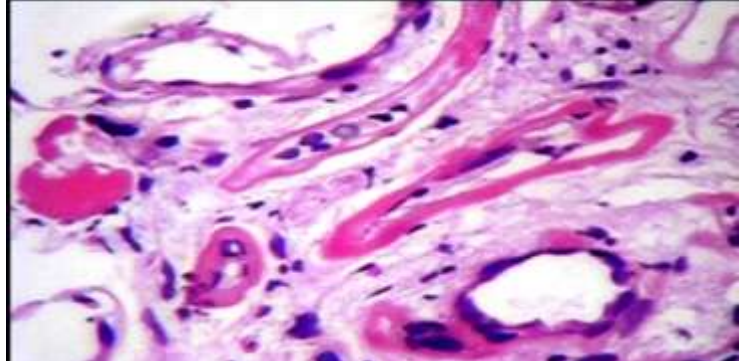
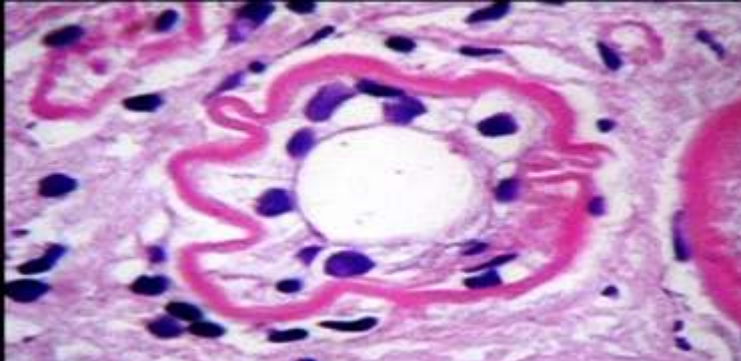


Arteries and arterioles contain deposits in close contact with their basement membranes

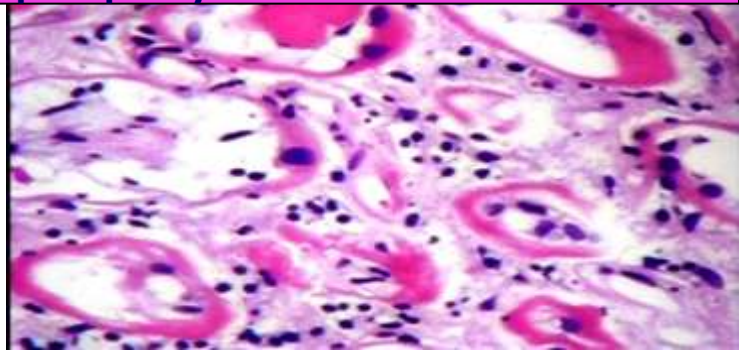
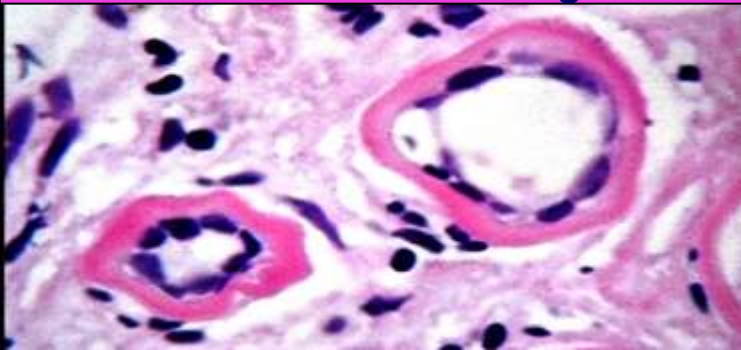


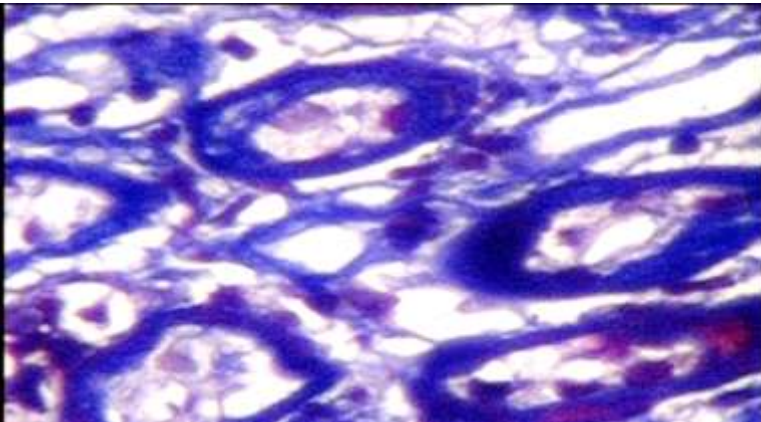




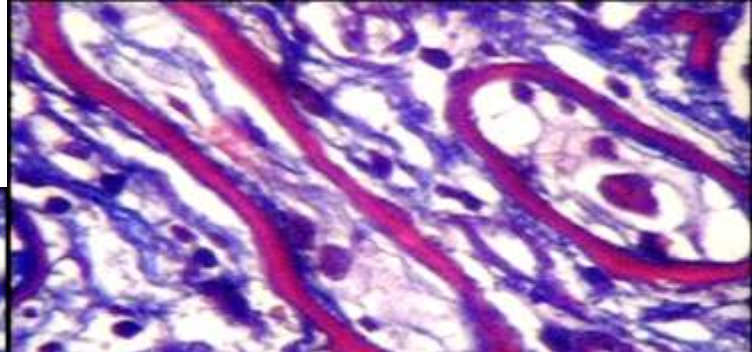


Light chain nephropathy



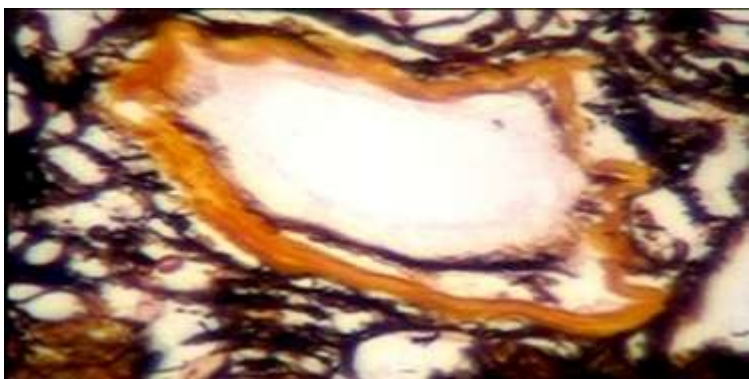
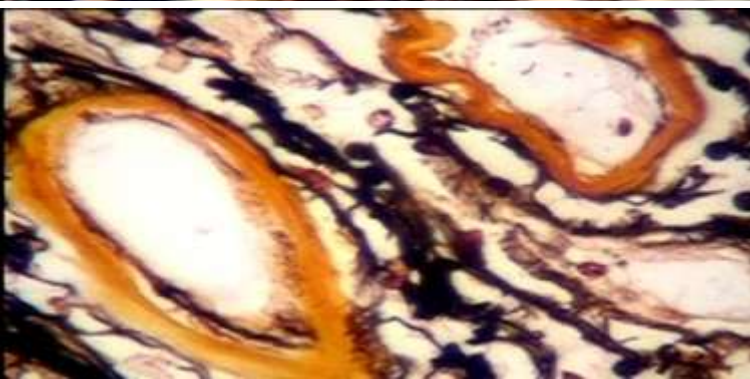
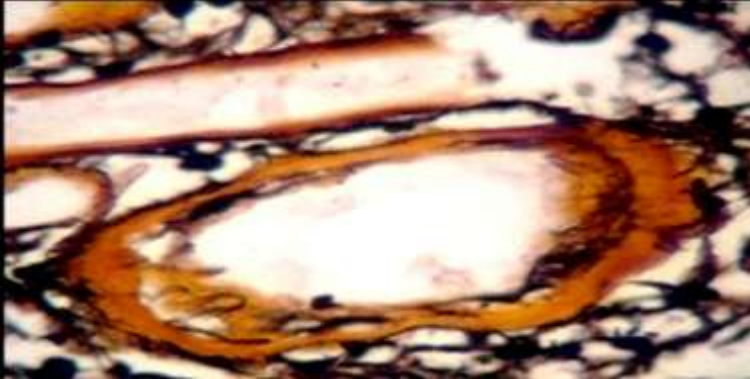


Atrophic tubules

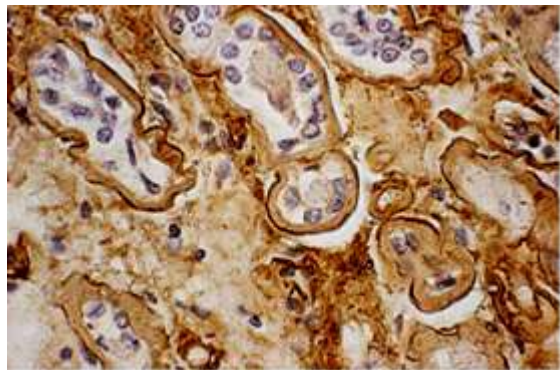


Light chain nephropathy



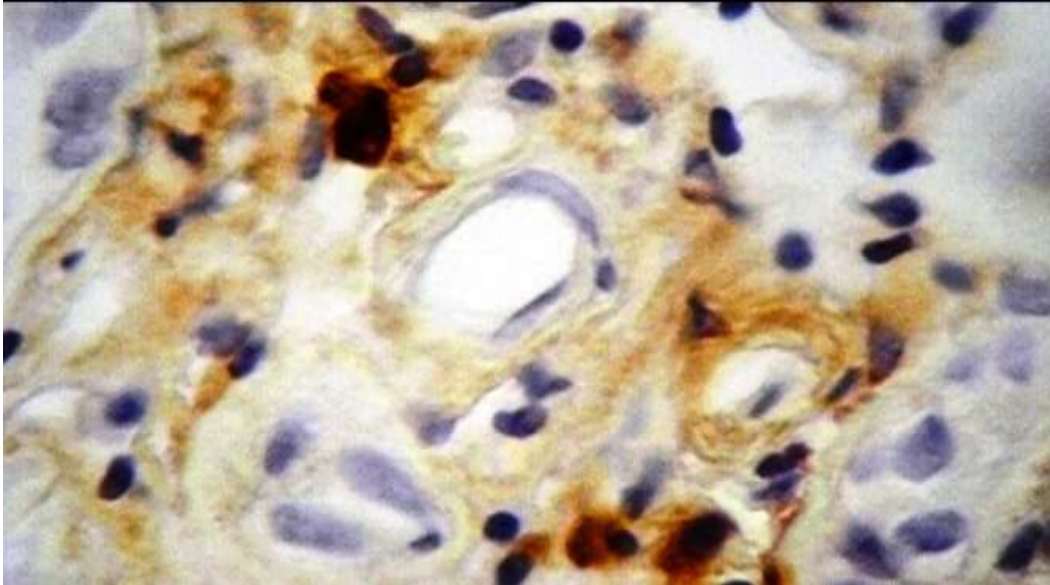


**Light chain deposition on the outer aspect of the tubular basement membranes.
(Immunohistochemistry for light chain, peroxidase anti-peroxidase stain,
diaminobenzidine as marker**



Light chain nephropathy

Kappa light chain



Light chain deposition disease

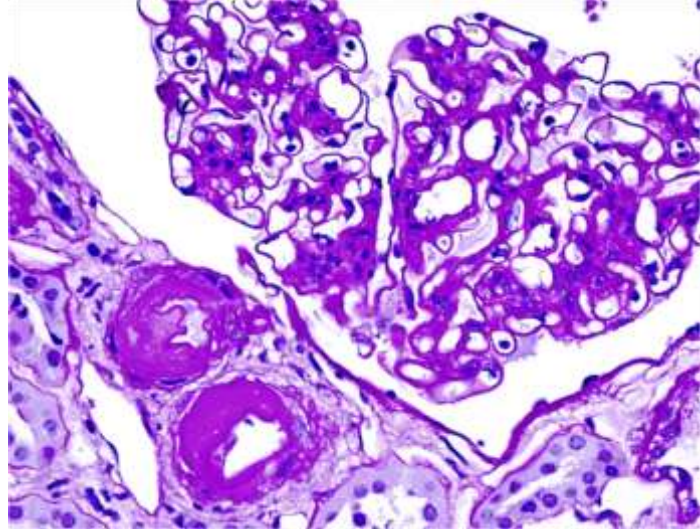
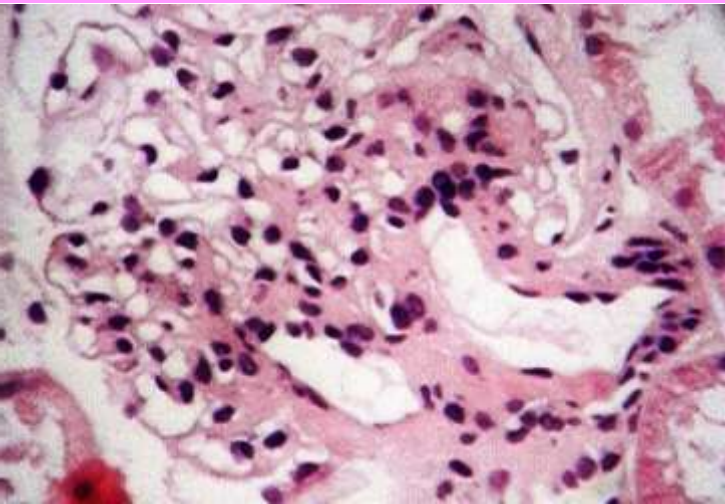
	Diabetic Nephropathy Class III	Light chain nephropathy
Uniformity of nodular size	nodules vary in size	uniform in size.
The silver stain	Argyrophilic	Less argyrophilic
E/M	-	fibrillar or microtubular ultrastructural pattern
Thickened basement membranes	+	
I/F	linear GBM & TBM pattern for both albumin & IgG	Kappa & Lamda

Pathologic differential diagnosis

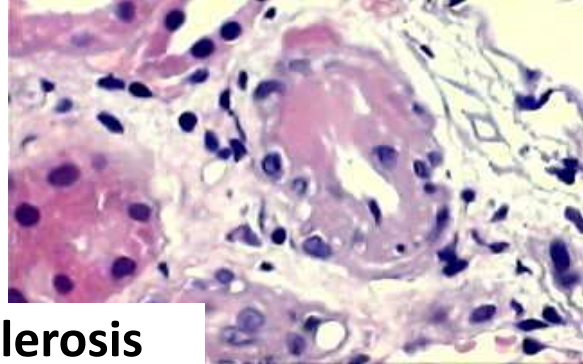
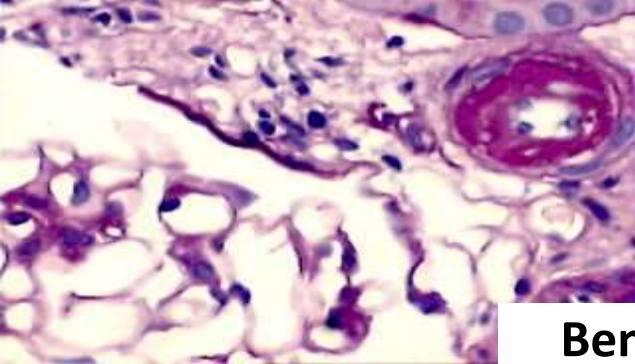
- Class I:
 1. Minimal change disease
 2. Membranous nephropathy
- Class II: Other causes of mesangial thickening (Fibrillary GN)
- Class III:
 1. Membranoproliferative pattern of GN
 2. Amyloidosis
 3. Light chain nephropathy
- Class IV:
 1. Hypertensive renal disease ←
 2. Advanced non diabetic renal disease

Hyaline Diabetic arteriolosclerosis

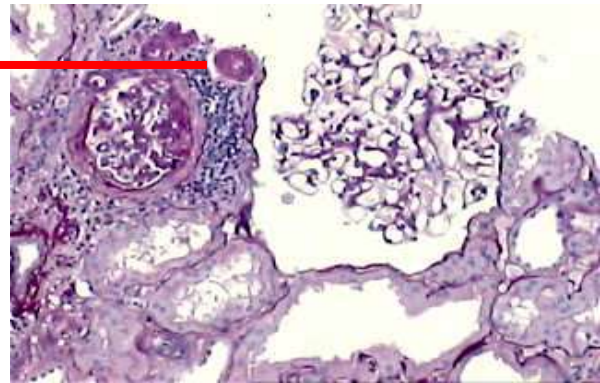
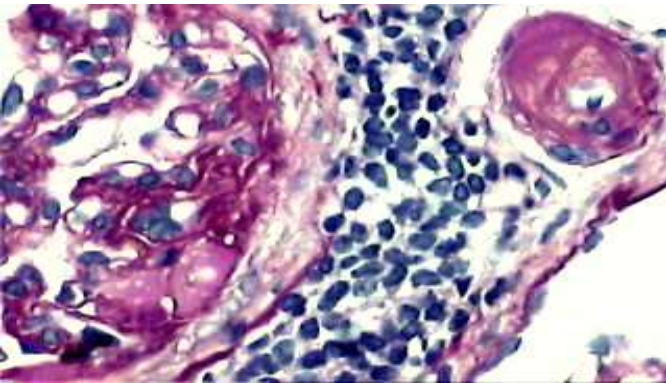
Hyaline efferent arteriole



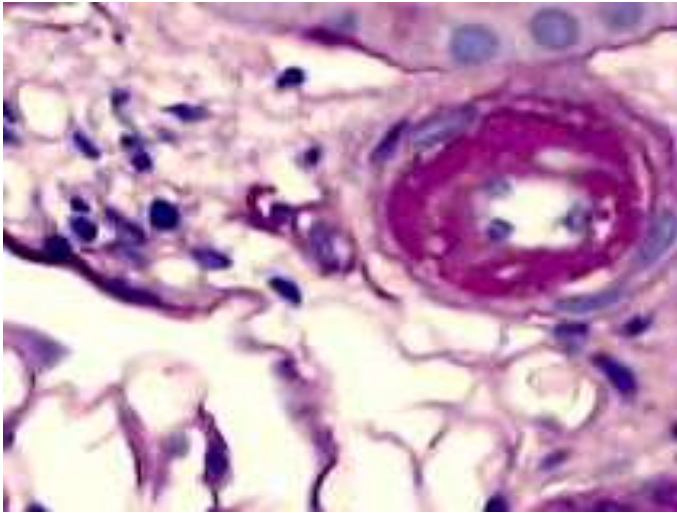
Hyaline afferent arterioles



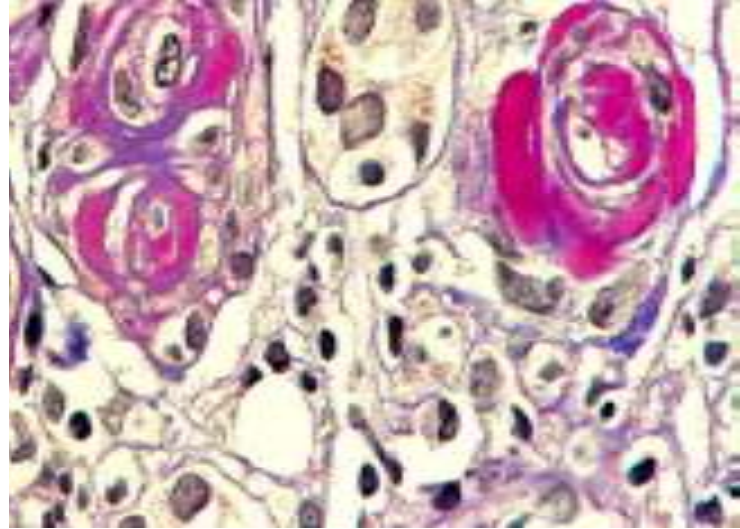
Benign nephrosclerosis



Hyaline arteriolosclerosis



Benign hypertension or diabetes



Chronic ciclosporine vasculopathy

3- Hypertensive renal disease

	Diabetic nephropathy	Hypertensive sclerosis
Diffusely thickened GBM and a general increase of mesangial matrix	+	+
Presence of kimmelstiel–wilson nodules,,	+	-
Linear staining of GBM and TBM for igg and albumin by IF	+	-
Hyalinization of the efferent arterioles	+	-